



## Cloud Point Extraction of Copper Using 4-(2-Chloroacetamido)-Salicylic Acid as a Complexing Agent

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### Abstract

A micelle-mediated procedure was presented for enrichment of Cu<sup>2+</sup> using 4-(2-chloroacetamido)-salicylic acid and Triton X-114 as complexing and extracting agents, respectively. The experimental parameters that affect the extraction were investigated and optimized. Good analytical features were achieved including limit of detection (0.25 µg L<sup>-1</sup>), limit of quantification (0.83 µg L<sup>-1</sup>), linearity (1.0-500 µg L<sup>-1</sup>) and reproducibility (2.2%). For 50.0 mL sample, the enrichment factor was 49.5. Most concomitant ions not interfere with Cu<sup>2+</sup> determination. The procedure was employed for preconcentration and determination of Cu<sup>2+</sup> in different samples (water, blood and urine) by flame atomic absorption spectrometry with satisfying results.

**Key words:** Cloud point extraction; copper; 4-(2-chloroacetamido)-salicylic acid; flame atomic absorption spectrometry

### 1. Introduction

Copper is one of the most essential elements at trace level for living cell. It has important industrial properties and applications. It acts as cofactors of many enzymes and plays a significant role in central nervous system development in addition to its important role in iron metabolism. In accordance with the World Health Organization (WHO), the maximum allowable limit of Cu in drinking water is 1000 µg L<sup>-1</sup> [1].

The most popular techniques for analysis of Cu<sup>2+</sup> are flame atomic absorption spectrometry (FAAS) [2], inductively coupled plasma - optical emission spectrometry (ICP-OES) [3] and UV-Vis

spectrophotometric techniques [4]. The major problems of these methods when applied to real samples are lack of sensitivity and selectivity. Applying of a separation step is usually essential before analysis to overcome these restrictions. Solid phase extraction (SPE) [5, 6], liquid-liquid extraction (LLE) [7], ion flotation [8] and cloud point extraction (CPE) [9, 10] are the most effective procedures for preconcentration of metal ions.

The CPE procedure has many advantages that make it superior over the other extraction operations. It is rapid, easy and eco-friendly as it employs surfactant as extracting agent instead of toxic organic solvent [11]. The technique of CPE of metal ions is based on

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three main steps: formation of hydrophobic metal/ligand complex, incorporation of the formed complex into the surfactant-rich phase [12]. Many organic compounds have been employed as complexing agents during CPE of  $\text{Cu}^{2+}$ . These include pyridylazo dyes [13], thiazolylazo dyes [14], dithiocarbamates [15], dithizones [16] thiocarbamides [17] and other ligands [18-21].

Although salicylic acid and its derivatives form stable complexes with many metal ions [22], their uses as ligands in CPE are limited. For this reason, the present work was aimed to study the CPE of  $\text{Cu}^{2+}$  using 4-(2-chloroacetamido)salicylic acid (CASA) as a complexing agent and Triton X-114 as surfactant, prior to FAAS determination. The procedure was optimized to achieve good analytical features and was applied for analysis of  $\text{Cu}^{2+}$  in real samples.

## 2. Experimental

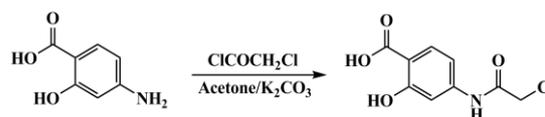
### 2.1. Reagents and solutions

Otherwise stated, all chemicals were obtained from Sigma-Aldrich (St. Louis, MO, USA). Stock solution of  $\text{Cu}^{2+}$  (1000 mg  $\text{L}^{-1}$ ) was prepared by dissolving appropriate amount of  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  (Merck, Darmstadt, Germany) in 2 mL of HCl and the volume was marked to 100 mL by double-distilled water. Sodium acetate/acetic acid buffer (pH 3.5-5.5) and ammonium acetate/acetic acid buffer (pH 6.0-8.0) were used to control pH.

### 2.2. Synthesis of 4-(2-chloroacetamido)salicylic acid

4-Aminosalicylic acid was chloroacetylated at its amino group through the reaction with chloroacetyl chloride. The reaction (Scheme 1) was carried out by stirring in acetone and potassium carbonate to afford 4-(2-chloroacetamido)-salicylic acid [23]. A suspension of 4-aminosalicylic acid (1.53 g, 0.01

mol) and sodium carbonate (1.38 g, 0.01 mol) was stirred in 20 mL acetone and then chloroacetyl chloride (0.80 mL, 0.01 mol) was added dropwise. The mixture was stirred for 2 h at ambient temperature and then diluted with 20 mL of water. The formed precipitate was separated and recrystallized. White crystals, yield = 84%, m.p. = 226-227°C (literature m.p. = 225-226°C [23]). IR (KBr): 3399, 3228 and 3213 (N-H and O-H), 1690 and 1662  $\text{cm}^{-1}$  (C=O).  $^1\text{H}$  NMR (DMSO- $d_6$ ): 4.27 (s, 2H,  $\text{CH}_2$ ), 7.04 (d,  $J = 9.00$  Hz, 1H, Ar-H), 7.32 (s, 1H, Ar-H), 7.73 (d,  $J = 9.00$  Hz 1H, Ar-H), 10.54 (s, 1H, NH), 11.36 (s, 1H, OH), 13.80 ppm (s, 1H, COOH). Analysis for  $\text{C}_9\text{H}_8\text{ClNO}_4$  (229.62): Calculated: C, 47.08; H, 3.51; N, 6.10%. Found: C, 47.21; H, 3.45; N, 6.17%.



**Scheme 1** Synthesis of 4-(2-chloroacetamido)salicylic acid

### 2.3. Apparatus

A Thermo-Nicolet IS10 FT-IR spectrometer (Nicolet Instrument Co, Madison, WI, USA) was employed for Fourier-transform infrared (FT-IR) analysis in KBr disc.  $^1\text{H}$ NMR spectrum in DMSO- $d_6$  was recorded at 500 MHz on a Jeol Delta 2-NMR (JEOL USA Inc., MA, USA). A pH meter (Metrohm 692, Herisau, Switzerland) was used to measure pH of solutions. A CH90-2 centrifuge (Hinotek Technology Co., Ltd. China) was employed to speed up the phase separation during CPE procedures. Phase separation during CPE procedures was accelerated using A CH90-2 centrifuge (Hinotek Technology Co., Ltd. China).

### 2.4. General procedure of CPE

In a 50 mL tube, aliquot (pH 6.0) containing  $\text{Cu}^{2+}$  ( $2.7\text{--}500.0 \mu\text{g L}^{-1}$ ),  $10^{-4} \text{ mol L}^{-1}$  CASA and 0.1 % (v/v) Triton X-114 were mixed. The mixture turns turbid upon addition of  $0.3 \text{ mol L}^{-1} \text{ Na}_2\text{SO}_4$  and the volume was made up to 50.0 mL by double-distilled water. Separation of the surfactant-rich phase was done by centrifugation (4000 rpm, 3 min). The tubes were kept in ice bath for 10 min to make the surfactant-rich phase more viscous than the aqueous phase was completely poured. The surfactant-rich phase was withdrawn with a micro-syringe and its volume was made to 1.0 mL using acidified ethanol then it was introduced to FAAS for determination of  $\text{Cu}^{2+}$ . The reagent blank was processed by the same procedure.

### 2.5. Application to real samples

Water samples were collected into acid washed polystyrene bottles, filtered, adjusted to pH 2.0 by  $\text{HNO}_3$  and storage at  $2^\circ\text{C}$  till analysis. Plasma samples were obtained from whole blood samples after centrifugation (4000 rpm, 10 min). Morning urine samples were collected polystyrene tubes. Plasma and urine samples were digested using previously optimized microwave procedure [6].

## 3. Results and discussion

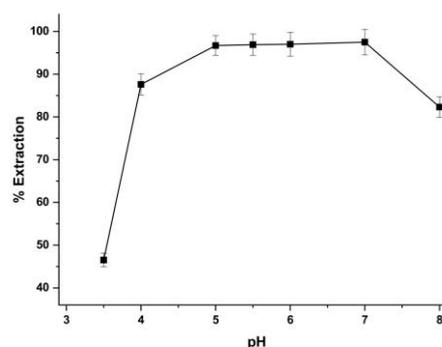
### 3.1. Optimization of CPE procedure

The different experimental factors (pH, ligand concentration, amount of surfactant, salting-out effect and centrifugation conditions) were investigated and optimized to achieve the best analytical features of the method.

#### 3.1.1. Effect of pH

The pH always has the greatest effect on the CPE process of metal ions as it impact stability of the formed complex [24]. The impact of pH on the preconcentration of  $\text{Cu}^{2+}$  was studied in the range of 3.0 – 9.0 by varying the solution pH using suitable

buffers. The results (Fig. 1) show that CPE of  $\text{Cu}^{2+}$  by the present procedure reaches the maximum uptake values (>95.0%) at pH range of 5.0-7.0. Below pH 5.0, the presence of high concentrations of  $\text{H}^+$  inhibits the complexation between  $\text{Cu}^{2+}$  and the ligand. The hydrolysis of  $\text{Cu}^{2+}$  and subsequent formation of metal hydroxides decreases the extraction at alkaline pHs. According to these findings, pH 5.0 was used in the subsequent trials.



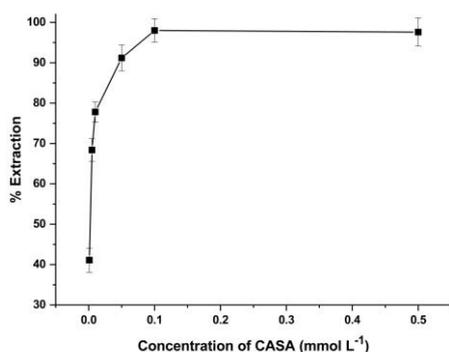
**Fig. 1** Effect of pH on CPE of  $\text{Cu}^{2+}$  [conditions: 50 mL solution,  $100 \mu\text{g L}^{-1} \text{ Cu}^{2+}$ ,  $10^{-4} \text{ mol L}^{-1}$  CASA, 0.1 % (v/v) Triton X-114 and  $0.3 \text{ mol L}^{-1} \text{ Na}_2\text{SO}_4$  at room temperature]

#### 3.1.2. Effect of ligand concentration

The obtainment of hydrophobic metal complex during CPE facilitates the extraction of metal and its incorporation into micelles [25]. CASA can form complex with metal ions through many function groups including hydroxyl, carbonyl and amide groups. The influence of amount of CASA on the extraction of  $\text{Cu}^{2+}$  was investigated (in the range of  $10^{-6}\text{--}5 \times 10^{-4} \text{ mol L}^{-1}$ ). The results in Fig. 2 show that the recovery of  $\text{Cu}^{2+}$  is directly proportional to the concentration of CASA and reach a quantitative and constant value at  $10^{-4} \text{ mol L}^{-1}$ . Therefore this amount was set as optimum value during the next investigations.

#### 3.1.3. Effect of Triton X-114

Surfactant is the critical reagent in CPE. It is necessary for micelles formation that incorporates metal complexes. Triton X-114 is the commonly used one in CPE owing to its relatively depressed cloud temperature, availability and safety [12]. The impact of Triton X-114 on the enrichment of  $\text{Cu}^{2+}$  was studied in the range from 0.05 to 0.2% (v/v). The results in Fig. 3 indicate that the separation efficiency of  $\text{Cu}^{2+}$  increases by increasing the amount of the



**Fig. 2** Effect of concentration of CASA on CPE of  $\text{Cu}^{2+}$  [conditions: 50 mL solution,  $100 \mu\text{g L}^{-1}$   $\text{Cu}^{2+}$ , pH 5.0, 0.1 % (v/v) Triton X-114 and  $0.3 \text{ mol L}^{-1}$   $\text{Na}_2\text{SO}_4$  at room temperature]

surfactant and reach a plateau at 0.1% (v/v), therefore the concentration of Triton X-114 was maintained at 0.1% (v/v) during the other experiments.

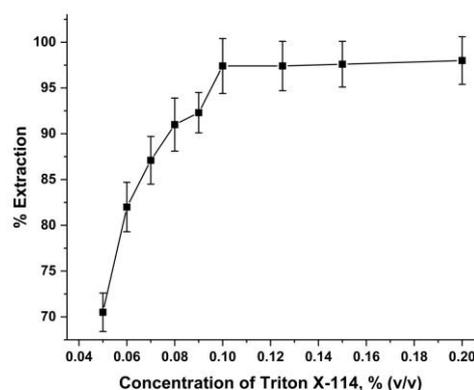
### 3.1.4. Effect of $\text{Na}_2\text{SO}_4$ :

Formation of cloudy solution takes place by heating above the cloud temperature of the surfactant used. Otherwise, addition of strong electrolytes such as  $\text{Na}_2\text{SO}_4$  can cancel the heating step making the process faster and energy saving [26]. The presence of certain electrolytes decreases the temperature at which the solution turns cloud by dehydration and subsequent aggregation of micelles. In the present study the effect of adding  $\text{Na}_2\text{SO}_4$  ( $0.1\text{--}0.5 \text{ mol L}^{-1}$ ) was investigated to obtain the best extraction efficiency of  $\text{Cu}^{2+}$ . As clarified in Fig. 4, addition of

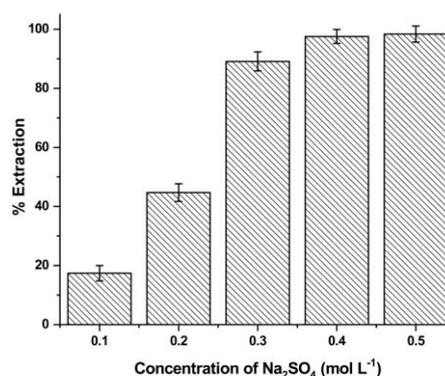
$0.3 \text{ mol L}^{-1}$  of  $\text{Na}_2\text{SO}_4$  lead to almost complete recovery of  $\text{Cu}^{2+}$ . So, the optimized procedure was performed in the presence of  $0.3 \text{ mol L}^{-1}$  of  $\text{Na}_2\text{SO}_4$ .

### 3.1.5. Centrifugation conditions

The impact of centrifugation rate (2000-4000 rpm) and time (3-10 min) was investigated to accelerate phase separation process. As shown in Table 1 centrifugation at 4000 rpm for 3 min lead to the fastest and most efficient separation.



**Fig. 3** Effect of concentration of Triton X-114 on CPE of  $\text{Cu}^{2+}$  [conditions: 50 mL solution,  $100 \mu\text{g L}^{-1}$   $\text{Cu}^{2+}$ , pH 5.0,  $10^{-4} \text{ mol L}^{-1}$  CASA and  $0.3 \text{ mol L}^{-1}$   $\text{Na}_2\text{SO}_4$  at room temperature]



**Fig. 4** Effect of concentration of  $\text{Na}_2\text{SO}_4$  on CPE of  $\text{Cu}^{2+}$  [conditions: 50 mL solution,  $100 \mu\text{g L}^{-1}$   $\text{Cu}^{2+}$ , pH 5.0,  $10^{-4} \text{ mol L}^{-1}$  CASA, 0.1 % (v/v) Triton X-114]

### 3.1.6. Selection of the solvent

Ethanol and acidified ethanol with nitric acid (5:1) were studied as diluents for the surfactant rich phase. The results show that acidified ethanol results in good recoveries (98.0-100%), while poor recoveries (81.0-84.0%) were obtained when ethanol was used. The low recoveries are probably due to incomplete dissolution of Cu/CASA complex by ethanol.

**Table 1. Effect of rate and time of centrifugation on the extraction of Cu<sup>2+</sup>**

Centrifugation rate	Centrifugation time	% Recovery
2000	3	69.0±4.2
	5	78.2±3.6
	10	94.5±3.9
3000	3	82.5±3.0
	5	95.0±4.1
	10	97.8±3.3
4000	3	99.5±2.0
	5	99.1±3.2
	10	98.9±3.5

Experimental conditions: Sample volume 50 mL, Cu<sup>2+</sup> 100 µg L<sup>-1</sup>, pH 5.0, CASA 1x10<sup>-4</sup> mol L<sup>-1</sup>, Triton X-114 0.1 % (v/v), Na<sub>2</sub>SO<sub>4</sub> 0.3 mol L<sup>-1</sup>.

### 3.2. Selectivity

The extraction of Cu<sup>2+</sup> by the proposed procedure was investigated in the presence of different diverse ions to examine the validity of the procedure for analysis of Cu<sup>2+</sup> in real samples. Aliquot (50.0 mL) containing 100.0 µg L<sup>-1</sup> and variable amounts of the diverse ion was subjected to the proposed procedure. The tolerance limit was estimated as the ultimate concentration of the diverse ion causing ±5.0% error in the recovery of Cu<sup>2+</sup>. The results summarized in Table 2 indicate that most studied species didn't interfere with the determination of Cu<sup>2+</sup> by the proposed procedure.

### 3.3. Analytical figures of merit

The analytical features of the optimized procedure were summarized in Table 3. The procedure exhibits linear range from 1.0 to 500.0 µg L<sup>-1</sup> with limit of detection (LOD = 3σ/S) of 0.25 µg L<sup>-1</sup> and limit of quantification (LOQ = 10σ/S) of 0.83 µg L<sup>-1</sup> where σ is the standard deviation of 10 blank measurements and S is the slope of calibration curve. The enrichment factor (EF), the ratio of the slopes of the calibration curves with and without CPE, was 49.5. The relative standard deviation (RSD) for determination of 50 µg L<sup>-1</sup> Cu<sup>2+</sup> (n=10) was 2.2%.

**Table 2. Tolerance limits of some ions on the determination of Cu<sup>2+</sup> (100 µg mL<sup>-1</sup>).**

Interfering ion	Tolerance limit (mg L <sup>-1</sup> )
Li <sup>+</sup> , Na <sup>+</sup> , K <sup>+</sup> , Cl <sup>-</sup> , NO <sub>3</sub> <sup>-</sup> , CH <sub>3</sub> COO <sup>-</sup> , HCO <sub>3</sub> <sup>-</sup>	>2,000
Mg <sup>2+</sup> , Ca <sup>2+</sup> , Ba <sup>2+</sup> , SO <sub>4</sub> <sup>2-</sup>	1000
Al <sup>3+</sup> , Ga <sup>3+</sup> , In <sup>3+</sup> , Cr <sup>3+</sup> , Cr <sup>6+</sup> , PO <sub>4</sub> <sup>3-</sup> , CO <sub>3</sub> <sup>2-</sup>	250
Mn <sup>2+</sup> , Cd <sup>2+</sup> , Ni <sup>2+</sup> , Fe <sup>2+</sup> , Co <sup>2+</sup> , Co <sup>3+</sup> , Zn <sup>2+</sup>	100
Ag <sup>+</sup> , Pb <sup>2+</sup> , Hg <sup>2+</sup>	50

**Table 3. Analytical features of the proposed procedure**

Parameter	Analytical feature
Linearity (µg L <sup>-1</sup> )	1.0-500.0
Regression equation	
<i>Slope</i>	2.9 x 10 <sup>-3</sup>
<i>Intercept</i>	0.02
Limit of detection (µg L <sup>-1</sup> )	0.25
Limit of quantification (µg L <sup>-1</sup> )	0.83
Reproducibility (RSD%)	2.2
Enrichment factor	49.5

### 3.4. Application and comparison with other CPE procedures

The applicability of the method was examined by the analysis of  $\text{Cu}^{2+}$  in water and biological samples. The results in Table 4 demonstrated the accuracy of the procedure as indicated by good recoveries of spiked samples (95.0-100.0%). The comparison of the preconcentration of  $\text{Cu}^{2+}$  with other CPE procedures [24, 27-31] is listed in Table 5. This comparison implies that our procedure exhibits lower LOD and wider analytical linearity than those of the other methods.

### 4. Conclusion

The CPE procedure presented here is a rapid, sensitive and selective for enrichment of  $\text{Cu}^{2+}$  in water, blood plasma and urine samples. Satisfactory analytical features were obtained in terms of linearity, LOD, LOQ, reproducibility and enrichment factor. Lower LOD was achieved compared to other CPE procedure. The procedure is accurate as indicated by analysis of spiked samples. The procedure is almost free from interferences and can be applied for preconcentration of  $\text{Cu}^{2+}$  from different matrices.

**Table 4. Analysis of real samples by the proposed CPE procedure**

Sample	Added ( $\mu\text{g L}^{-1}$ )	Found ( $\mu\text{g L}^{-1}$ ) <sup>1)</sup>	Recovery (%)
Tap water	-	BDL	-
	10.0	9.8±0.4	98.0
	20.0	19.4±0.7	97.0
Urine (normal human)	-	32.5±1.7	-
	10.0	42.0±2.0	95.0
	20.0	52.3±2.4	99.0
Blood plasma (normal human)	-	745.0±29.6	-
	100.0	841.5±33.9	96.5
	200.0	945.0±36.5	100.0

**Table 5. Comparison of the present procedure with other CPE procedures for spectrophotometric determination of  $\text{Cu}^{2+}$**

Complexing agent	Detection	Samples	EF	LOD ( $\mu\text{g L}^{-1}$ )	Linearity ( $\mu\text{g L}^{-1}$ )	RSD	Ref.
2-(3-ethylthioureido)benzoic acid	FAAS	Water, biological and food samples	50.8	0.71	2.4-500	2.1	[24]
N-phenylbenzohydroxamic acid	FAAS	Water and hair samples	45.0	1.0	5.0-220	1.9	[27]
3-amino-7-dimethylamino-2-methylphenazine	FAAS	Spice samples	69.0	0.3	1.0-200	1.8	[28]
2-amino-4-(m-tolylazo)pyridine-3-ol	Spectrophotometry	Water, biological and food samples	125.0	1.2	4.0-115	1.3	[29]
Diethyldithiocarbamate	Spectrophotometry	Water and cola drink samples	17.0	0.7	Up to 500	2.9	[30]
2-(5-bromo-2-pyridylazo)-5-(diethylamino) phenol	FAAS	Water samples	25.0	1.5	10.0-100	Not provided	[31]
4-(2-chloroacetamido)-salicylic acid	FAAS	Water, urine and blood plasma	49.5	0.25	1.0-500	2.2	The present study

**Conflict of interest:**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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